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Metabolizing new synthetic pathways

***Kristala Prather* from the Massachusetts Institute of Technology talks to *Nature Chemical Engineering* about her path into metabolic engineering, the influence of her industrial experience and how the existing gap with academia is more an opportunity rather than a problem.**

Can you briefly tell us about your research and what brought you into it?

My early research focus was really the direct result of the fusion of my doctoral thesis and my work at Merck. One of the areas I worked on at Merck was biocatalysis, where our group was responsible for identifying microbes and enzymes to perform specific reactions that were difficult to conduct with the appropriate specifications by chemical catalysis. These were always single-step reactions in the middle of a longer synthesis scheme. When I considered this in the context of my training in metabolic engineering, it sparked my interests in designing multistep biocatalytic cascades, that is, in designing novel biosynthetic pathways.

Today, my group thinks about our research from two different perspectives. Broadly speaking, we seek to use biological systems – microbes – to produce chemical compounds. However, this is motivated by a desire to displace fossil-derived feedstocks as the inputs to the materials that serve to benefit humanity. A particular interest in the group is in designing new biosynthetic routes to chemical compounds of interest, including organic acids useful as industrial chemicals as new monomers for sustainable materials. This work is complemented by several approaches to improve productivities and yields. We have developed methods for dynamic metabolic engineering, and employed transcription-factor-based biosensors to build microbial systems that operate more efficiently through response to substrate and intermediate concentrations. In this way, we can think about broadening the utility of biology for chemistry, leading to more sustainable processes.

Synthetic biology started to be considered from an engineering perspective around the early 2000s. How has the field evolved since then?

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In the early days of synthetic biology, there was a heavy focus on defining the key principles. This led to a lot of work on, for example, the specification of genetic parts and devices, and work on characterization and standardization. New computational tools and approaches were also developed. That work continues, but there are far more examples of synthetic biology 'in action' – that is, the translation of these principles into applications. I think the current challenges revolve around scaling up into commercial processes, as well as successfully applying the principles to more complex biological systems.

This is strictly related to the chemical engineering curriculum, where one of the core subjects is kinetics and reactor design – it was one of my favorite undergraduate classes. Among other topics, this course covers design principles for reactions in series, parallel or a combination thereof. This constitutes the perfect description for a microbial cell: it is a collection of molecules formed from the action of thousands of reactions occurring in parallel and in series. Thus, the core principles from chemical engineering kinetics and reactor design can be applied to the biochemical reactions that take place inside a cell. Applying those principles allows engineers to make design decisions that lead to cells capable of synthesizing specific compounds with high yields and productivities.

You worked in industry at DuPont and Merck & Co. before starting your research group. What are some of the differences between working in industrial and academic settings?

I have such appreciation for the time I was able to spend in industry before starting my academic career. It all started with a visit to the Experimental Station at DuPont in my fourth year of graduate studies. One of the senior scientists there complimented my work for the impact he felt it would have on the field, but he also shared with me his view that my motivation for the work was all wrong. I had established objectives I thought were important to industry, but he told me quite directly that I was way off the mark. Suitably humbled, I became very appreciative for his insight, and it drove me to seek an industrial job, this time at Merck Research Labs before transitioning to academia. I learned so much, especially about people management (a necessary but often underappreciated task for new faculty), and about how chemical engineering was being practiced in industry.

There are some very real differences between academia and industry, but I am of the opinion that this is a feature, not a bug. Companies need to fail fast (and preferably not at all), which means keeping researchers on the critical path. I learned so much from failure while I was in graduate school, and my students do as well. But more importantly, we have had exciting new projects emerge when we have veered off the critical path. I value the ability to explore in academic research, but typically, academic levels of exploration are not appropriate for industry. This, to me, is a gap worth preserving, even as we work to better articulate it.

How have you incorporated biological principles into the courses that you teach? The Massachusetts Institute of Technology has the Undergraduate Research Opportunities Program, can you tell us about it?

For many years, I taught our introductory chemical engineering class, featuring material and energy balances. I have always sought to incorporate example problems of a biological nature, emphasizing the ways in which complex cells and cellular systems are still bound by the laws of conservation of mass and energy. Earlier in my career, I introduced new modules into our bioprocess engineering laboratory, based on my research, that are still in use today.

The Undergraduate Research Opportunities Program (UROP) is a marvellous way to incorporate undergraduate students into our research labs. Students can join labs as early as their first semester on campus, although I typically require students to wait until January, when they can work in the laboratory over four weeks without classes competing. Most students will work directly with a graduate student or postdoc, but those who stick with it are often operating at the level of a second- or third-year graduate student by the time they enter their senior year. I think the value of UROP goes well beyond learning lab skills — it teaches research skills and strengthens the analytical abilities and judgements of students.

Can you tell us about a major challenge you have faced in your career? Based on that, do you have any advice for new scientists and engineers?

This one is easy to answer. As much as I cherish the time I spent in industry (and I would not do it any differently), starting my academic career after four years away from academic research was very difficult. Restrictions on confidentiality and intellectual property made it essentially impossible for me to bring any projects from my time at Merck. My graduate research was also considered 'old' by then, which meant starting an entirely new research program. I am still not sure how I tackled it, but I know that it would not have been possible without the support of my family. And, of course, the brilliance of my early graduate students and postdocs was essential. I'll give my advice in the form of an anecdote.

My early years were quite stressful and, honestly, I was not sure I was meant to be an academic. One day, I was visiting with family and friends, including two tenured faculty members at another university. As I was complaining about the difficulties and the associated stress, my sister-in-law said: "I listened to [her husband] saying these same things while he was going through tenure. Why don't you all just quit?" My response was immediate: "Because people who get this far have made it, because we can't quit."

If you have made it this far, it is because you have the talent and the determination to be successful in science and engineering. That does not come by accident — it is a testament to the time and effort you have dedicated to your training. If this is really what you want to do, you can.

Congratulations on your new role as Head of the Department of Chemical Engineering. Can you tell us about an achievement that you are most proud of and why?

I think I would have to say it is recognition as a MacVicar Faculty Fellow at the Massachusetts Institute of Technology. This award is described as "the highest honor for undergraduate teaching" at my university, but I like to think that it encompasses the work I do with my graduate students and postdocs as well. My research is very important to me, but, honestly, I can think of several companies where I could pursue similar lines of work — and with more resources. But the potential to educate, encourage and support the next generation of scientists and engineers in an educational setting gives me a chance to amplify my impact far beyond what I could ever personally do as an individual. Our world is facing so many challenges on so many levels. We need a continual supply of brilliant minds and generous hearts to conquer them. I cannot think of any higher honor than serving in a capacity that enables me to facilitate their emergence.

Interviewed by Alessio Lavino